

REVIEWS

A clinicopathological classification of granulomatous disorders

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Abstract

Granulomatous disorders comprise a large family sharing the histological denominator of granuloma formation. A granuloma is a focal compact collection of inflammatory cells, mononuclear cells predominating, usually as a result of the persistence of a non-degradable product and of active cell mediated hypersensitivity. There is a complex interplay between invading organism or prolonged antigenaemia, macrophage activity, a Th1 cell response, B cell overactivity and a vast array of biological mediators. Differential diagnosis and management demand a skilful interpretation of clinical findings and pathological evidence. They are classified into infections, vasculitis, immunological aberration, leucocyte oxidase deficiency, hypersensitivity, chemicals, and neoplasia.

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Granulomatous disorders comprise a large family sharing the common histological denominator of granuloma formation. Granulomas may be confluent or discrete; the degree of necrosis is variable; the cell components differ; and the presence or absence of Schaumann bodies and of calcification are distinctive. A clinicopathological synthesis provides the most secure foundation.

Granuloma formation

A granuloma is a focal, compact collection of inflammatory cells, mononuclear cells predominating; it is usually formed as a result of the persistence of a non-degradable product of active hypersensitivity. The granuloma is the end result of a complex interplay between invading organism or antigen, chemical, drug or other irritant, prolonged antigenaemia, macrophage activity, a Th1 cell response, B cell overactivity, circulating immune complexes, and a vast array of biological mediators (fig 1). Areas of inflammation or immunological reactivity attract monocyte macrophages which may fuse to form multinucleated giant cells, and a transformation of macrophages to epithelioid cells. The granuloma is an active site of numerous enzymes and cytokines, and, with aging, fibronectin and numerous progression factors. There is a close relationship between activated macrophages bearing increased expression of major histocompatibility complex (MHC) class II molecules and CD4+ Th1 lymphocytes. These T helper cells recognise protein peptides presented to them by antigen presenting cells bearing MHC class II molecules. The T cell induces interleukin-1 on the macrophage and thereafter a cascade of chemotactic factors promote granulomagenesis. Interferon gamma (IFN- γ) increases the expression of MHC class II molecules on macrophages, and activated macrophage receptors carry an Fc fraction of IgG to potentiate their ability to phagocytose. The end result is the epithelioid granuloma which progresses under the impact of transforming—and platelet—derived growth factor towards fibrosis.¹⁻³

T cell activation also requires the B7:CD28/CTLA:4 costimulatory pathway. With CD28 mediated costimulator, there is active T cell proliferation; without it, there is ignorance, anergy, and apoptosis.⁴ Overstimulation of Th1 relative to Th2 cells leads to pronounced cell mediated hyperactivity, tissue destruction, and granuloma formation. This is slowed down by B7-1 or B7-2 antagonists. The opposite occurs

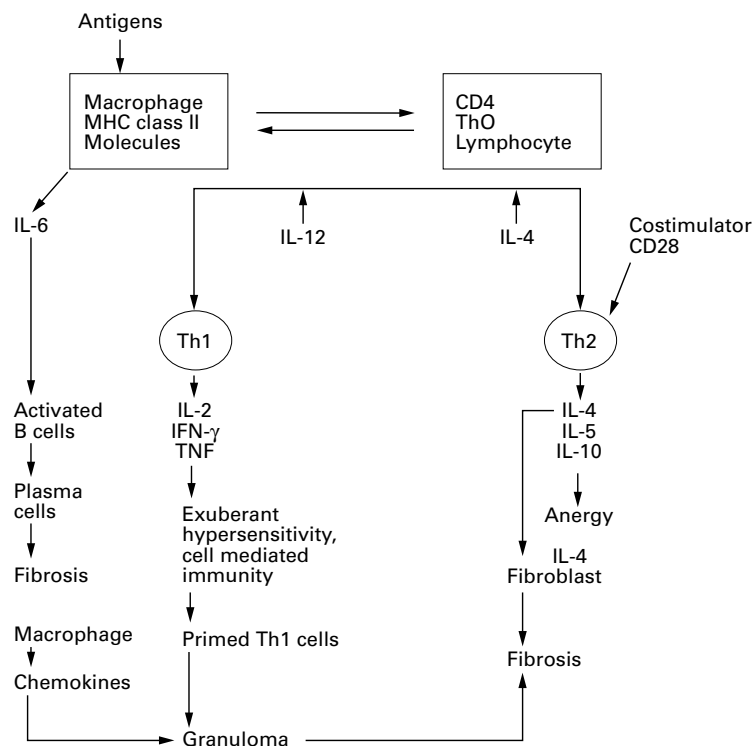


Figure 1 The cytokine network (IFN- γ = interferon gamma; IL = interleukin; MHC = major histocompatibility complex; TNF = tumour necrosis factor).

Table 1 Classification of granulomatous disorders

(1) Infections	(2) Vasculitis	(5) Hypersensitivity Pneumonitis
Fungi	Wegener's	Farmers' lung
Histoplasma	Necrotising sarcoid	Bird fanciers'
Coccidioides	Churg-Strauss	Mushroom workers'
Blastomyces	Lymphomatoid	Suberosis (cork dust)
Sporothrix	Polyarteritis nodosa	Bagassosis
Aspergillus	Bronchocentric	Maple bark strippers'
Cryptococcus	Giant cell arteritis	Paprika splitters'
Protozoa	Systemic lupus erythematosus	Coffee bean
Toxoplasma		Spatlese lung
Leishmania	(3) Immunological aberrations	
Metazoa	Sarcoidosis	(6) Chemicals
Toxoplasma	Crohn's disease	Beryllium
Schistosoma	Primary biliary cirrhosis	Zirconium
Spirochaetes	Hepatic granulomatous disease	Silica
T pallidum	Langerhan's granulomatosis	Starch
T carateum	Orofacial granulomatosis	Talc
T pertenuae	Peyronie's disease	
Mycobacteria	Blau's syndrome	(7) Neoplasia
M tuberculosis	Hypogammaglobulinaemia	Carcinoma
M leprae	Histiocytosis X	Reticulosis
M kansasii	Immune complex disease	Pinealoma
M marinum		Dysgerminoma
M avian	(4) Leucocyte oxidase defects	Seminoma
BCG vaccine	Chronic granulomatous disease of childhood and adults	Reticulum cell sarcoma
Bacteria		Malignant nasal granuloma
Brucella		
Yersinia		(8) Miscellaneous infections
		Whipple's disease
		Cat scratch
		Lymphogranuloma
		Kikuchi
		Buruli ulcer

when Th2 seems to override Th1 influences. There is anergy and apoptosis, which may be reversed by CD28 agonists.

Immunohistochemistry has revealed a continuing role for fibronectin, collagen, integrin receptors, and transforming growth factors in that slippery road from a healthy granulomatous response to irreversible and unchangeable fibrosis.

Classification

This large family of granulomatous disorders comprise infections, vasculitis, immunological upsets, leucocyte oxidase defect, hypersensitivity, chemicals, and neoplasia (table 1). Differential diagnosis and management demand a skilful interpretation of clinical findings and histology⁵ (table 2).

(1) INFECTIONS

Infections are the commonest causes of disseminated granulomatous disease (table 2). Some experts regard an infection as the root cause of all such disorders but that it still remains undetected in some; over the past decade advances in molecular diagnostic techniques have allowed identification of causal organisms that were previously unrecognised. For instance, cat scratch disease is due to *Bartonella henselae* and Whipple's disease due to

Tropheryma whippeli. Infective causes are suspected but not yet established for sarcoidosis, Crohn's disease, primary biliary cirrhosis, Kikuchi's disease, Langerhans' granulomatosis, and chronic granulomatous disease of childhood. The aetiology, course, prognosis, and treatment of granulomatous infections have been reviewed elsewhere.⁶ The present review draws attention to some which currently give rise to diagnostic confusion.

Mycobacterial infections

This large family of mycobacteria is responsible for granulomatous disorders of many different systems (table 3). The invading organism is met by a vigorous cell mediated hypersensitivity reaction involving macrophages, Th1 lymphocytes, and their cytokines. The polymerase chain reaction (PCR) has uncovered mycobacterial DNA in sarcoid tissue and mycobacterial RNA has been extracted from sarcoid spleen by liquid phase DNA/RNA hybridisation giving rise to false speculations concerning the aetiology of sarcoidosis.

Swimming pool (fish tank) mycobacterial granuloma

Mycobacterium marinum causes swimming pool (fish tank) granuloma. Although the primary

Table 2 Histological comparison of various granulomatous disorders

Features	Sarcoid granuloma	Necrosis	Schaumann bodies	Interstitial cellular inflammation	Cavities	Vasculitis	Mediastinal adenopathy
Sarcoidosis	+	—	+++	±	±—	±	+
Tuberculosis	+	++ Caseation	±—	±	+	±	+(Primary)
Extrinsic allergic alveolitis	+(Acute stage)	—	±	++	—	++	—
Beryllium disease (chronic)	+	±	++	++	—	—	—
Wegener's granulomatosis	±	++ Infarction	—	++ Giant cell	++	++	Rare
Lymphomatoid granulomatosis	±	++	—	++ Immature	±	±	Rare
Bronchocentric granulomatosis	+	+	—	Eosinophil	±	±	Rare
Necrotic sarcoid granulomatosis	+	++	—	++ Mature	+	++	±
Churg-Strauss granulomatosis	++	++	—	++ Mature	—	++	Rare

Table 3 Granulomatous mycobacterial infections

Clinical disorder	Common site	Mycobacteria
Tuberculosis	Lung Meninges Skin Intestine	<i>M tuberculosis</i>
Leprosy Tuberculoid Lepromatous	Skin Nervous system Soft tissues	<i>M leprae</i>
Bronchopneumonia Lymphadenitis Osteomyelitis AIDS	Lung Lymph node Bone Joints Meninges	<i>M avium</i> complex; <i>M kansasii</i> ; <i>M xenopi</i> ; <i>M simiae</i> ; <i>M scrofulaceum</i> ; <i>M chelonae</i> ; <i>M malmoense</i> ; <i>M fortuitum</i>
Swimming pool and fish tank granuloma	Skin Soft tissues Draining lymph nodes	<i>M marinum</i> or <i>M balneum</i>
Buruli ulcer	Skin Soft tissues	<i>M ulcerans</i>

skin infection may be inconspicuous, the draining lymph nodes are extensively involved and caseous. A similar microscopic picture, with conspicuous plasma cell infiltration, is associated with granulomas due to other opportunistic mycobacteria. Fish tank granulomas develop in persons with minor abrasions who dip their hands in tropical fish tanks. Usually a solitary granuloma, nodule, or pustule forms, which may ulcerate or suppurate; but, multiple lesions may extend along the line of lymphatic vessels.

Biopsy specimens that are cultured on Löwenstein-Jensen medium at room temperature yield pigmented mycobacterial colonies in 2–4 weeks. The response to treatment is variable and not dramatic. Antituberculous drugs, cotrimoxazole, and high doses of minocycline have been advocated.

The development and application of molecular techniques such as PCR may in the future allow more accurate diagnosis.

Beware also of sea urchin granuloma of the feet in bathers and fishermen stepping on sea urchins.

Buruli ulcer

Mycobacterium ulcerans is the cause of chronic, relatively painless, cutaneous Buruli ulcers. The disease is most prevalent in Africa and Australia. The organism causes extensive undermined ulcers on the extensor surface of the extremities. The centres of the ulcers are necrotic, and the edges are undermined; the organisms are usually found at the periphery, where granulation tissue is most extensive. While it is relatively easy to diagnose Buruli skin ulcers on the basis of clinical features and histological findings, microbiological identification of the causal mycobacteria may sometimes be quite difficult, requiring long periods of culture. Newer techniques such as gas phase chromatography are becoming useful for identification of the acid-fast bacilli in low count subcultures.

Granulomatous mycoses

Granulomatous fungal infections mimic sarcoidosis worldwide. It is important to recognise or exclude fungi localised to one system or disseminated; in particular, granulomatous fungal meningitis needs to be distinguished from sarcoidosis by all available techniques (table 4).

Whipple's disease

George Hoyt Whipple's single case report described a 37 year old medical missionary who presented with fever, polyarthrititis, and steatorrhoea.⁷ It is a chronic multisystem granulomatous disorder affecting middle aged white males, presenting with fever, polyarthrititis, weight loss, and diarrhoea progressing to malabsorption. There may be hepatosplenomegaly.

Table 4 Granulomatous mycoses

Fungus	Clinical diagnosis	Immunopathology	Method of diagnosis	Treatment
<i>Nocardia</i> sp <i>Actinomyces</i> sp	Actinomycosis	Pneumonia Granuloma Fibrosis	Microscopy Culture	Penicillin Minocycline
<i>Coccidioides immitis</i>	Coccidioidomycosis	Bronchopneumonia Cavitation Chronic granuloma	Culture CFT ELISA Tube precipitin	Amphotericin B Flucytosine Fluconazole
<i>Cryptococcus neoformans</i>	Cryptococcosis	Pneumonia Infarction Abscess Granuloma fibrosis	Microscopy Culture	Fluconazole Amphotericin B Flucytosine
<i>Candida</i> sp	Candidiasis Moniliasis	Abscess Necrosis Granuloma	Microscopy Culture	Nystatin Amphotericin B
<i>Sporothrix schenckii</i> <i>Histoplasma capsulatum</i>	Sporotrichosis Histoplasmosis	Granuloma Pneumonia Cavitation Granuloma	Microscopy, culture CFT Microscopy Radioimmunoassay	Amphotericin B Amphotericin B Ketoconazole Rifampicin
<i>Aspergillus fumigatus</i>	Aspergillosis	Necrotising granuloma	Culture Microscopy Precipitins	Amphotericin B Itraconazole
<i>Paracoccidioides brasiliense</i>	South American blastomycosis	Bronchopneumonia Pulmonary cavities Exudate → granuloma	Culture Sputum CFT	Amphotericin B Flucytosine Sulfadiazine
<i>Blastomyces dermatitidis</i>	Blastomycosis	Microabscess Pneumonia	Culture	Amphotericin Itraconazole Flucytosine
<i>Phialophora</i> sp <i>Madurella</i> sp	Chromoblastomycosis Mycetoma	Cutaneous granuloma Subcutaneous granuloma	Culture Grains in pus	Ketoconazole Itraconazole Dapsone

CFT = complement fixation test. ELISA = enzyme linked immunosorbent assay.

megaly and generalised lymphadenopathy. Biopsy of lymph node, liver, or small intestine reveals foci of PAS staining foamy macrophages in all sites. The PAS positive material within these histiocytes corresponds with lysosomes containing bacilliform bodies. Electron microscopy reveals rod shaped bacilli, termed Whipple bacilli or *T. whippelii* or Whipple associated bacterial organism.⁸ The nucleic acids extracted from an endoscopic biopsy specimen of the proximal small bowel of a patient with Whipple's disease has been subjected to nucleotide sequencing and amplification by the PCR. The resulting PCR product from the bacterial 16S ribosomal DNA was then the subject of a computer database search for the rRNA sequences most similar to it. It showed that Whipple bacilli were most likely to belong to the family of Gram positive bacteria of the rhodococcus, streptomyces and arthrobacter genera, and more weakly related to mycobacteria. PCR primers for *T. whippelii* now provide a helpful diagnostic technique.⁹

Cat scratch disease

Cat scratch disease or fever is also known as benign lymphoreticulosis or regional granulomatous lymphadenitis. It only occurs in humans, especially those who are scratched or bitten by kittens and then develop regional lymphadenitis proximal to the site of injury. Primary involvement is that of the lymph nodes, which first show lymphoid hyperplasia. Later, scattered granulomas with central areas of necrosis coalesce to form abscesses. *B. henselae* is the responsible Gram negative bacillus. It is identified by PCR hybridisation and indirect fluorescent antibody assay.

The histopathological features of cat scratch disease are not diagnostic and may be mistaken for tularaemia, lymphogranuloma venereum, syphilis, brucellosis, atypical mycobacterial infections, fungal infections, and toxoplasmosis. Warthin-Starry silver staining is used to detect *B. henselae*, which may be present in the early phase of the disease. A skin test antigen has been made from lymph node pus. It is inoculated intradermally, and the degree of induration and erythema is measured at 48 hours.

The cat scratch antigen skin test is positive in about 90% of patients who are clinically suspected of having the disease. This test will become redundant when techniques for amplifying specific nucleotide sequences with PCR come into general use. There is no well recognised response to antibiotics, and recovery usually occurs without treatment.

Kikuchi's disease

This disorder was described in 1972 by a Japanese pathologist and is characterised by lymphadenitis showing focal reticulum cell hyperplasia, nuclear debris, and phagocytosis.⁹ Clinically there is localised tender cervical lymphadenopathy with an upper respiratory prodrome. Most cases occur in women under the age of 30 years. Kikuchi's disease occurs world wide and has been often confused with toxoplasmosis, cat scratch disease, tuberculo-

sis, infectious mononucleosis, and non-Hodgkin's lymphoma. A viral aetiology is strongly suspected on the basis of clinical features, although serological and ultrastructural studies have not yet identified an infectious agent.¹⁰

(2) VASCULITIS

The family of vasculitic granulomatoses comprise Wegener's granulomatosis, necrotising sarcoidal granulomatosis, Churg-Strauss syndrome, lymphomatoid granulomatosis, polyarteritis nodosa, bronchocentric granulomatosis, giant cell arteritis, and systemic lupus erythematosus. They may occasionally be confused with sarcoidosis and hypersensitivity pneumonitis (extrinsic allergic alveolitis), so a careful clinicopathological synthesis is essential (table 5).

Granulomatous vasculitis is a small group of systemic disorders of unknown cause and obscure pathogenesis. It has long been considered that both humoral and cellular immune mechanisms are involved, and a cascade of cytokines may influence their course. The future management may indeed depend upon manipulation of this cytokine network.

(3) IMMUNOLOGICAL ABERRATIONS

The causal agent or antigenic insult remains unrecognised in many granulomatous disorders so they are clumsily lumped together as a group in which an immunological upset plays a major part. They are waiting for the cause to be found or the immune process better understood. Within this category are sarcoidosis, primary biliary cirrhosis, hepatic granulomatous disease, Langerhans' granulomatosis, orofacial granulomatosis, Peyronie's disease, Blau's syndrome, hypogammaglobulinaemia, and immune complex disease.

Sarcoidosis

Sarcoidosis is a multisystem disorder of unknown cause(s) most commonly affecting young adults, and frequently presenting with hilar lymphadenopathy, pulmonary infiltration, ocular and skin lesions. The diagnosis is established most securely when well recognised clinicoradiographic findings are supported by histological evidence of widespread epithelioid granulomas in more than one system. Multisystem sarcoidosis must be differentiated from local sarcoid tissue reactions. There is imbalance of CD4:T8 subsets, an influx of Th1 helper cells to sites of activity, hyperactivity of B cells, and circulation of immune complexes. Markers of activity include raised levels of serum angiotensin converting enzyme and monocyte chemoattractant protein-1; abnormal calcium metabolism; a positive Kveim-Siltzbach skin test; intrathoracic uptake of radioactive gallium; and abnormal fluorescein angiography.

The course and prognosis correlate with the mode of onset. An acute onset usually heralds a self limited course of spontaneous resolution whereas an insidious onset may be followed by relentless progressive fibrosis. Corticosteroids relieve symptoms, suppress the formation of

Table 5 Differential diagnosis of pulmonary granulomatous vasculitis

Features	Wegener's granulomatosis			Churg-Strauss syndrome	Necrotising sarcoid granulomatosis	Bronchocentric granulomatosis		
	Classic	Limited	Lymphomatoid granulomatosis			Asthma	No asthma	Sarcoidosis
F:M	M > F	Equal	M slightly more frequent	Same	Same	Same	Same	Same
Decade of incidence	50	50	30-50	50	30 and 40	30	60	30 and 40
Presentation	Sinusitis Rhinitis Epistaxis	+	Cough Dyspnoea Haemoptysis Arthralgia	Bronchitis Asthma Pneumonia	Fever Cough Pleurisy Malaise	Asthma	Cough Pleurisy Dyspnoea	Insignificant symptoms
Ulcerated nose and nasal septum	+	+	-	-	-	Bronchiectasis Bronchial obstruction Eosinophilia	-	Only when associated with lupus pernio and SURT
Saddle nose								
Chest radiography								
Opacities	+	+	+	+	+	Particularly in upper lobes		+
Cavitation	++	+	-	-	-	Pulmonary fibrosis		Infiltration
Hilar adenopathy	-	-	-	-	-	-	-	+
Kidneys	+	-	Renal vasculitis	-	-	-	-	Nephrocalcinosis
Ocular	+	±	-	-	-	+	+	-
Allergy	+	±	-	+	-	-	-	-
Skin lesions	+	-	+	Rare	Rare	-	-	+
Central nervous system	+	-	+	-	-	-	-	+
Cardiac	+	-	-	-	-	-	-	+
Characteristics	ESR ANCA	-	-	Eosinophilia	-	Hypersensitivity to aspergillus Eosinophilia		Raised SACE
Granulomas	±	±	Very rare	Infrequent	Always	+	+	Always
Vasculitis	++	++	Always	Always	++	±	±	Inconspicuous
Necrosis	Prominent and resemble infarcts		Prominent	Prominent	Prominent	+	+	Inconspicuous
Treatment	Cyclophosphamide Steroids		Cyclophosphamide Azathioprine	Steroids Azathioprine	Steroids Azathioprine	Corticosteroids		Steroids Azathioprine
Prognosis	Guarded		Poor	Poor	Good	Good		Good

+ Present, ++ prominent, - absent, ± inconspicuous.

ANCA: antineutrophil cytoplasm autoantibody; ESR = erythrocyte sedimentation rate; SACE = serum angiotensin converting enzyme; SURT = sarcoidosis upper respiratory tract.

granulomas (including Kveim-Siltzbach granulomas), and normalise both levels of serum angiotensin converting enzyme and the uptake of gallium. A synthesis of clinical features, radiology, histology, biochemical changes, and immunological abnormalities helps to distinguish it from non-specific local sarcoid tissue reactions.

Tumour necrosis factor alpha (TNF- α) is a proinflammatory cytokine widely recognised and implicated in inflammatory disorders including sarcoidosis. It is inhibited by tumour necrosis factor receptor (TNF-R) which is recognised in two forms p55 (CD120a) and p75 (CD120b) receptors. This TNF-TNF-R balance in favour of inhibition may represent a homeostatic mechanism which protects the patient from excessive TNF production in sarcoidosis. TNF-R p55 is increased in stage I more than stage II/III sarcoidosis, suggesting that homeostasis is responsible for a more benign outcome at this early stage of sarcoidosis.¹¹

Crohn's disease

The commonest cause of granulomatous inflammation in the gastrointestinal tract is Crohn's disease. This reaction seems to centre on the blood vessels of the intestinal wall causing multifocal gastrointestinal infarction. There may be associated lung changes, including pulmonary vasculitis, granulomatous interstitial lymphocytic infiltration, alveolitis, and interstitial fibrosis. Alveolar macrophages may show an increased spontaneous superoxide anion production. An increase in CD4 cells is found in bronchoalveolar fluid and even in sputum. Serum antibody increases include antireticulin antibody, antisaccharomyces cerevisiae antibody (ASCA), and p-antineutrophil cytoplasmic antibody (ANCA). There is concordance between ASCA and p-ANCA. ASCA occurs in up to 60% of patients, particularly with familial Crohn's disease; and ASCA is evident in 20% of first degree relatives.^{5 12 13}

Primary biliary cirrhosis (PBC)

PBC is a chronic non-suppurative destructive cholangitis¹⁴ in which epithelioid granulomas are in close association with bile ducts. It predominates in women of the reproductive years of age and it is distinguished by the presence of serum mitochondrial antibodies. It is classified as an autoimmune disorder and overlaps with other autoimmune disorders including Sjogren's syndrome, rheumatoid arthritis, the calcinosis Raynaud oesophagus scleroderma telangiectasia (CREST) syndrome, scleroderma, and systemic lupus erythematosus.

Cholangiocyte apoptosis is responsible for bile duct destruction due to aberrant expression of the major autoantigen, the E2 subunit of the pyruvate dehydrogenase complex. There is some evidence that PBC with high titres of antinuclear antibodies progress slower and result in a better prognosis than those with low titre or negative antinuclear antibodies.

PBC histology may be granulomatous or alternatively eosinophilic. Could this be due to the predominant influence of either the Th1

cytokine cascade producing granulomas or the Th2 cascade causing an eosinophilic response?

The aetiology of PBC remains unknown. There are similarities between *Escherichia coli* and mitochondrial components; cross reactivity between bile duct mitochondria and bacteria is a possibility. An increased incidence of Gram negative urinary tract infections is recognised in PBC. It has been likened to the chronic graft-versus-host rejection with similar structural change in the bile ducts, lacrimal and pancreatic ducts, which have a high concentration of HLA class II antigens on the epithelial surface.

A differential diagnosis of some hepatic granulomatous disorders is appended (table 6).

Langerhans' cell granulomatosis

The term Langerhans' cell granulomatosis refers to proliferative disorders of histiocytes, previously referred to as histiocytosis X. It encompasses a group of disorders of unknown aetiology characterised by granulomatous infiltration of the lungs, bone, skin, lymph nodes, and brain.⁵⁻¹⁵ The clinical conditions have been known by several names, based on the type of presentation, sites of involvement, rate of progression, and degree of associated immune dysfunction. They include eosinophilic granuloma, Letterer-Siwe disease, and Hand-Schüller-Christian disease. They are different expressions of the same basic disorder, in which the proliferation of Langerhans' cells results from disturbances in immunoregulation.

Langerhans' histiocytes are bone marrow derived monocyte macrophage cells; they include Langerhans' epidermal cells, Kupffer's cells in the liver, osteoclasts, and alveolar macrophages. They are human leucocyte antigen DR positive functioning macrophages that present antigen to T cells and play a part in cell mediated immunity. Unlike histiocytes, Langerhans' cells can be stained immunohistochemically for S-100 protein and OKT-6.

Lung biopsy reveals a mixed cellular exudate, foam cells, eosinophils, and characteristic

X bodies (Birbeck granules) in macrophages. Langerhans' or X bodies are an ultrastructural feature in 90% of patients. They are identical to the granules in Langerhans' epidermal cells and consist of intracytoplasmic rod, plate, or cup-like pentalaminar structures. The presence of these tennis racket shaped ultrastructural Birbeck granules is diagnostic of the disorder. They have surface adenosine triphosphate activity identifiable by gold fluorescence. These diagnostic cells are readily found by bronchoalveolar lavage, and this technique may make lung biopsy unnecessary. It may also be a likely means of detecting a possible causal agent in the future.

Orofacial granulomatosis (Melkersson-Rosenthal syndrome)

This is a rare granulomatous disorder of the mouth and adjacent tissues, involving the oral mucosa, gum, lips, tongue, pharynx, eyelids, and skin of the face.

Melkersson described an association between facial oedema and facial paralysis.¹⁶ Rosenthal added the features of lingua plicata or scrotal tongue.¹⁷ Other clinical features include granulomatous cheilitis, oedema of the gums and scalp, salivary gland dysfunction, granulomatous blepharitis, trigeminal neuralgia, Raynaud's phenomenon, and even chronic hypertrophic granulomatous vulvitis.¹⁸⁻¹⁹ Patients with this disorder do not have chest radiography changes, nor uveitis; and the Kveim-Siltzbach skin test is negative. This rare disorder may be immunologically mediated for the T cell receptor B (TCRVB) repertoire is restricted.²⁰ This is evident in oral mucosal lymphocytes, and it is associated with a local T cell clonal expansion. These features suggest a delayed type reaction in response to an unknown antigen. Local cytokine release may be responsible for the granulomatous reaction.

Blau's syndrome

Edward Blau is a Wisconsin paediatrician who described a multisystem granulomatous disease of the skin, eyes and joints, resembling childhood sarcoidosis.²¹ The histology may be indistinguishable so paediatricians should be aware of significant differences between the two disorders. The most frequent manifestation is swelling of the wrists, fingers, ankles, and elbows in the first decade of life. Because of the granulomatous histology of synovial tissue, it may be misdiagnosed as tuberculosis of bone. There may be progression of flexion contractures of joints (camptodactyly) due to post-inflammatory fibrotic scarring at insertion points of finger and toe flexor tendons. There is a granulomatous red papular eruption of the skin with a butterfly distribution on the face. It coincides with exacerbations of the granulomatous iritis.

Blau's syndrome is a multisystem disorder in which there is no lung involvement; this may be an important difference from other granulomatous disorders.

The granulomas of Blau's syndrome are indistinguishable from those of sarcoidosis by light microscopy or by immunocytochemistry.

Table 6 Differential diagnosis of some diseases with hepatic granulomas

Disease	Diagnostic aids
Sarcoidosis	Chest radiograph; Kveim; SACE
Tuberculosis	Bronchoalveolar lavage Tuberculin skin test Bronchoalveolar lavage Acid-fast staining Isolation organism
Brucellosis	Blood culture Agglutinin titre
Berylliosis	Industrial exposure Chest radiograph
Syphilis	Treponema test
Leprosy	Race; lepromin skin test
Histoplasmosis	Complement fixation test Chest radiograph
Infectious mononucleosis	Blood film, monospot, IgM Epstein-Barr antibodies
AIDS	Poorly formed granulomas Acid-fast and fungal stains HIV test
Primary biliary cirrhosis	Mitochondrial antibody
Lymphomas	Chest radiograph; lymph node biopsy Computed tomography

SACE = serum angiotensin converting enzyme.

However asteroid, Schaumann and conchoid bodies, organisms, calcification and crystalline inclusions, necrosis and fibrin deposition are absent.

Granulomatous hypogammaglobulinaemia

On rare occasions, one wonders whether the patient has hypogammaglobulinaemia or sarcoidosis or both. Confusion arises since both conditions may present with multisystem granulomas, hypersplenism, and poor cellular immunity. The hypogammaglobulinaemia may be selective IgA deficiency or a more widespread deficiency of IgA, IgG, and IgM. There is bedside clinical evidence of loss of both B and T lymphocyte function, which is also evident by in vitro lymphoproliferative assays.

(4) LEUCOCYTE OXIDASE DEFECTS

Killing of bacteria depends on a burst of respiratory enzyme activity which leads to the production of hydrogen peroxide and superoxide in phagocytes. Neutrophils in chronic granulomatous disease of childhood (CGDC) are unable to kill some ingested bacteria because they are deficient in enzymes needed for this superoxide respiratory burst. These defective enzymes may be nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, myeloperoxidase, cytochrome B, pyruvate kinase, glucose-6-phosphate dehydrogenase, or the lack of lysozyme or lactoferrin, each perhaps contributing a different clinical profile. The classical X linked disorder occurs in boys aged about 5 years, presenting with hepatosplenomegaly, generalised lymphadenopathy, weeping granulomatous skin lesions, and diffuse miliary lung infiltration. The history is of multisystem sarcoid granulomas. There is more than one X linked form and also more than one autosomal recessive variety, for there is more than one mechanism for initiating oxidative metabolism.²² Patients with CGDC suffer from infections with catalase-producing staphylococci and enterobacteria. Organisms that lack catalase supply the neutrophil with the hydrogen peroxide for their own destruction. Thus catalase negative organisms, such as pneumococci or streptococci, present no problem to these patients. Neutrophil leucocytes of normal patients with bacterial infections reduce nitroblue tetrazolium from colourless to form blue-black formazan granules in the cytoplasm. This fails to occur in the leucocytes of CGDC children or in the mothers of the X linked variety. The X linked variety is due to mutations in the gene for the gp 120-phox subunit of the phagocyte cytochrome b, an essential component of superoxide-generating NADPH oxidase. Most patients have undetectable levels of cytochrome b and no phagocyte NADPH oxidase activity. This gives rise to life threatening bacterial and fungal infections in infancy. Some patients have a milder course because they retain some cytochrome NADPH oxidase activity.

IFN- γ has proved helpful in enhancing host defences and thereby reducing the incidence of life threatening infections, particularly those infections characterised by persistence in macrophages (toxoplasmosis, leishmaniasis, and mycobacteriosis).⁹

Thrasher *et al* used an adenovirus vector expressing p47-phox to transduce patients' defective monocytes.²³ Nitroblue tetrazolium staining indicated that NADPH oxidase activity was restored to those cells. This technique offers a rapid means for molecular diagnosis and points to a therapeutic future of gene transduction.

Chronic granulomatous disease in adults (CGD)

Chronic granulomatous disease is being recognised more commonly in adults. Although it is still rare it should be excluded in adults with unexplained granulomas or infections.²⁴ Antibiotic prophylaxis and the use of IFN- γ has allowed children, mostly with reduced gp91-phox (X91-CGD), to present for the first time in young adult life. The NBT is insufficient as a screening test for it may give values close to normal in adults. It should be complemented by chemoluminescence or cytochrome b reduction. This is important because of the benefits of earlier diagnosis and treatment, infection prophylaxis, and genetic counselling.

(5) HYPERSENSITIVITY PNEUMONITIS (EXTRINSIC ALLERGIC ALVEOLITIS)

Repeated inhalation of various antigens may provoke a granulomatous inflammatory response in the bronchoalveolar spaces and interstitium giving rise to a family of pulmonary disorders termed hypersensitivity pneumonitis or extrinsic allergic alveolitis. The best recognised members of the family are farmers' lung, pigeon breeders' lung, and humidifier fever. The clinical picture may be acute and explosive, subacute and insidious, or chronic and protracted; cough and dyspnoea on exertion, fatigue, and weight loss are common. The end stage is characterised by irreversible restrictive lung function and cardiac failure. Pathogenesis involves a complex interplay of circulating immune complexes, immediate hypersensitivity, and exuberant cell mediated immunity. The diagnosis is established by a history of occupational exposure; suggestive clinical and radiological changes; and demonstration of precipitating serum antibodies. Mid to late inspiratory crackles and the absence of finger clubbing are notable features. An increase in CD8+ T cells in bronchoalveolar fluid is also noteworthy.

(6) CHEMICALS

There are four granuloma forming chemicals: beryllium, zirconium, silica, and talc.^{5 13}

Beryllium disease mainly affects the lungs following inhalation of soluble, finely particulate beryllium and its salts. Direct implantation may also give rise to skin ulcers and nodules. Pulmonary disease may be acute or chronic (CBD); the former is a chemical pneumonitis after massive exposure to fumes whereas CBD is a chronic granulomatous disorder. It is due to occupational exposure in a variety of industrial processes, alloy workers, ceramic workers, and in space and atomic engineers. The respiratory symptoms are in keeping with diffuse and nodular fibrosis of the lungs, with pleural thickening and late cystic changes. The granu-

loma contains a variety of inclusion bodies, Schaumann and asteroid; they are end products of the actively secreting epithelioid cells. Diagnostic criteria include history of exposure; consistent clinicoradiological features, granulomatous histology, and tissue analysis for beryllium.

Zirconium

This chemical was recognised as a cause of deodorant axillary granulomas in sensitised individuals. A 1:10 000 solution of zirconium chloride or nitrate inoculated intradermally produced a palpable nodule, which, on biopsy, revealed sarcoid tissue. This was specific for zirconium hypersensitivity. This skin test is very similar to the Kveim-Siltzbach skin test for sarcoidosis. Zirconium is no longer in deodorants so these axillary granulomas are no longer seen. However it is of some academic interest that there are four granulomatous disorders in which skin tests behave in this peculiar fashion, mimicking the Kveim-Siltzbach test. The other two were the beryllium patch test and the Mitsuda skin test in lepromatous leprosy.

Silicosis

Inhalation of pure silica may be followed by dense nodular and rarely diffuse pulmonary fibrosis. The silica granuloma is readily identified by the presence of crystalline birefringent crystals in macrophages with foreign body rather than Langhans-type giant cells.

Pulmonary talc granulomatosis

This is due to the inhalation of talc in the form of talcum powder or by prolonged repeated intravenous administration of pentazocine (75% talc).

(7) NEOPLASIA

There is often a granulomatous component in malignant disease. Sarcoid granulomas may be found in various tumours and in their draining lymph nodes, particularly those draining carcinoma of the lung, stomach, and uterus. They may also be found in tumours that have been treated by radiotherapy or chemotherapy, since treatment may produce a granulomagenic substance which spreads to draining lymph nodes.

There is diagnostic confusion between sarcoidosis and Hodgkin's disease, in which multi-system granulomas are also observed. The difficulty usually arises in the interpretation of small specimens of aspiration liver biopsies, or the occasional patient in whom the spleen is replaced by sarcoid tissue obliterating tumour tissue. Intrathoracic Hodgkin's disease most frequently affects the upper mediastinum rather than hilar lymph nodes, and it is predominantly unilateral. The hilar nodes tend to fuse with the right cardiac border whereas in sarcoidosis they stand away from the cardiac border. Both disorders show depression of cell mediated immunity. In Hodgkin's disease, the Kveim-Siltzbach test is negative and serum angiotensin converting enzyme levels are raised in only about 10% of patients, compared with 60% in sarcoidosis.

(8) MISCELLANEOUS

Granulomatous angiitis

Granulomatous angiitis is a multifocal chronic inflammatory disorder in which magnetic resonance imaging may show multiple discrete granulomas. The initial diagnosis may suggest an infection, such as tuberculosis or toxoplasmosis, or alternatively intravascular lymphomatosis.

Granuloma annulare

These skin lesions may be single, multiple, or disseminated with flat centre and a well delineated edge. The histology is of a necrobiotic area with palisading granulomas in giant cells. A similar histological reaction may be seen in rheumatoid disease and with a ruptured sebaceous cyst.

Actinic granuloma

This disfiguring condition is a granulomatous reaction to excessive sun exposure. There is debate whether it is a distinct clinicopathological entity or a variant of granuloma annulare or multiforme and necrobiosis lipoidica. Treatment with isotretinoin has prevented development of new granulomas and produced almost complete resolution of established lesions.

Granulomatous rosacea

Rosacea has been described as the curse of the Celts.²⁵ It is commoner in women, aged 30 to 50 years. There is a background diathesis of flushing and blushing, upon which develops erythema, papules, pustules, telangiectasia, furuncles on the face, neck and v-shaped area of the chest. Granulomatous or lupoid rosacea nodules may also involve the lower eyelids. Histology reveals perifollicular and perivascular granulomas; it needs to be distinguished from micronodular sarcoidosis, particularly since both conditions may be associated with iritis and conjunctivitis. Minidose isotretinoin, 2.5 mg to 5 mg daily, oral tetracycline, or metronidazole may be helpful for lupoid rosacea.

Other

Do not be surprised if the histological report of a removed sebaceous cyst indicates a granuloma. The same granulomatous reaction occurs in chalazion, dermoid, panniculitis, sea urchin spine injury, tattoos, or malakoplakia. It indicates a vigorous macrophage Th1 reaction to the antigenic insult, involving cytokines and other biological mediators (fig 1). It indicates a good defence and a satisfactory outcome against the antigenic aggression.

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